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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/20, 47/26, 9/16 | A1

(11) International Publication Number: WO 98/11878

(43) International Publication Date: 26 March 1998 (26.03.98)

(21) International Application Number: PCT/FI97/00548

(22) International Filing Date: 16 September 1997 (16.09.97)

(30) Priority Data:
08/715,825 19 September 1996 (19.09.96) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: DIRECTLY COMPRESSIBLE LACTITOL AND METHOD

(57) Abstract

The invention relates to a directly compressible lactitol granulate and lactitol tablets made therefrom. The granulate comprises lactitol and a physiologically acceptable, non-cariogenic binder, which may be a non-cariogenic sugar alcohol, a polymerized reducing sugar, and alkali carboxymethylcellulose, a hydrogenated starch hydrolysate, a hydroxypropylcellulose, a physiologically acceptable cellulose derivative, polyvinylpyrrolidone, gum arabic or another physiologically acceptable gum. The preferred binder is lactitol. The invention also relates to a method of producing a directly compressible lactitol granulate, which can be used in tabletting contexts. The produced tablets exhibit high hardness and low friability. They are non-cariogenic and manifest the taste profile and metabolic properties of lactitol.

DIRECTLY COMPRESSIBLE LACTITOL AND METHOD

This invention relates to a directly compressible lactitol granulate. The granulate comprises lactitol and a physiologically acceptable, non-cariogenic binder. The preferred binder is a non-cariogenic sugar alcohol such as lactitol. The invention also relates to a method of producing a directly compressible lactitol granulate, which can be used in tabletting contexts; the granulate exhibits acceptable flow characteristics and has an appropriate compression profile. The granulate manifests the taste profile, metabolic and non-cariogenic properties of lactitol. The invention also relates to tablets, which contain lactitol and which exhibit high hardness, low friability, are non-cariogenic and manifest the taste profile and metabolic properties of lactitol.

The most commonly used sweetener for food and pharmaceutical contexts is sucrose. Sucrose is used for its well-known sweetening properties and also for bulking purposes. Although a wide variety of alternate sweeteners are available, sucrose is generally considered to be the optimum sweetener with regard to taste profile and technological properties. However, sucrose has been implicated as a contributory factor in many diseases including hypertension, coronary heart disease, arterial sclerosis and dental caries. These health concerns have led health care professionals to analyze the effects of sucrose and its prominent role in the diet.

Lactitol is a sweet-tasting dimeric sugar alcohol, which is derived by the catalytic hydrogenation of lactose. Commercially lactitol is available as either a mixture of mono and dihydrates and anhydrous lactitol, or as the pure monohydrate and pure anhydrous forms.

The use of lactitol is attractive because of certain taste and technological characteristics which it exhibits. In particular, lactitol has a number of attributes which make it potentially quite useful as a tabletting excipient, including, but not limited to:

1. the pure monohydrate form is essentially non-hygroscopic, which enhances its ability to be a stable, free-flowing product, which has the potential to provide shelf stable tablets;
2. lactitol offers an aqueous solubility which is similar to sucrose, which contributes to its ability to provide a smooth, non-chalky mouthfeel and suitable release of active ingredients;
3. lactitol contributes only 2 kcal/g;
4. lactitol is metabolized independent of insulin requirement and exhibits a glycemic index of essentially zero;

5. lactitol is non-cariogenic; and
6. unlike many sugar alcohols, lactitol exhibits a minimal negative heat of solution (cooling effect), which can interfere with desired flavor systems.

The combination of lactitol's attributes (non-hygroscopicity, solubility, caloric value, metabolic utilization, dental and organoleptic) clearly set lactitol apart from other crystalline sugar alcohols and other alternative bulk sweeteners. For example, while mannitol (a common tabletting excipient) is essentially non-hygroscopic, contributes 1.6 kcal/g, is non-cariogenic and is metabolized independent of insulin, mannitol contributes a noted cooling effect and a low solubility, which often results in a chalky mouthfeel. Sorbitol and xylitol contribute noted cooling effects and moderate hygroscopic properties. Maltitol is moderately hygroscopic and exhibits a moderate insulin requirement and 3 kcal/g. Isomalt, like mannitol, exhibits a low solubility which can impact on tablet mouthfeel.

One context in which lactitol has been heretofore utilized with only limited success is as a constituent in tablets. U.S. Patent No. 5,534,555 to Meygelaars et al. discusses a lactose/lactitol combination mix (not a granulate), which is represented to be "directly compressible". However, the mix is not as free flowing and does not have all of the handling benefits of a granulate, is cariogenic, and does not fully exploit the benefits of lactitol as may be manifested in a tablet context.

In pharmaceutical contexts, tablets are used for bringing active substances into a size, shape and texture that can be dosaged, chewed, sucked, swallowed whole or dissolved in water for drinking. In food contexts, tablets can take the form of compressed, fruit or mint flavored confections, which consist of a sweetener(s), flavor(s) and optionally color and acid.

Because of its taste and other properties as described above, lactitol is a potentially attractive constituent in tablets for both food and pharmaceutical purposes. Other polyols have been utilized in tablet contexts as diluents, flavoring agents and binders, but lactitol has not heretofore been used extensively in this context.

Tablets can be formed by compression or by molding. Simple compression techniques have been known for centuries; in 1577 Hieronymous Bosch, in his Kreuttenbuch, describes a simple press, used for making medicines. The sugar coating of "pills" was first attributed to Jean de Renou in 1606, and one of the first patents for the manufacture of "pills and medical lozenges" was granted to one Thomas Brockedon in Great Britain in 1843. Many types of tablets exist including chewable tablets, lozenges, effervescent, coated centers, film coated

tablets, enteric coated tablets, time release tablets (for release of ingredients over time), multi-layered tablets and others.

Modern compression tabletting techniques - irrespective of the type (and ultimate shape of the end product) - utilize a piston-like device with three stages in each cycle: (1) filling - adding the constituents of the tablet to the compression chamber; (2) compression forming the tablet; and (3) ejection - removing the tablet. The cycle is then repeated. A representative tablet press is a MANESTY EXPRESS 20 rotary press, manufactured by Manesty Machines Ltd., Liverpool, England, and many others are available.

In order to make tablets, preferably all ingredients - or at least the carrier or diluent which typically makes up the bulk of the tablet - must have certain physical characteristics, including the ability to flow freely, and acceptable cohesion (or compressibility). Because many materials have some, or none, of these qualities, techniques must be developed to impart these characteristics to the constituents. In this context, "free flowing" means that the particles to be compressed must enter the compression chamber as discreet particles. While particles which are not "free flowing" can be used in tabletting contexts, they can be utilized only if force feeders or other mechanical means are utilized to move the particles. Such methods add to the expense of the process, and decrease the efficiency considerably; therefore, they are rarely used. "Compressible" means the particles form a tablet after compression and do not remain in a powdered or substantially powdered form.

Two critical criteria in the quality of a tablet are crushing strength (or hardness) and friability. The resistance of the tablet to chipping, abrasion, or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Hardness is measured by determining lateral breaking strength (expressed in Newtons or Strong Cobb Units wherein 7 N = 1 S.C.U.) exerted on a single tablet at the moment of rupture. A representative hardness tester is the Model HT-300 manufactured by Key International, Inc. Acceptable hardness depends on the desired mouthfeel and the expected end use and packaging conditions of the tablet, but in most contexts, tablet hardness must be greater than about 10 S.C.U. to be commercially useful.

Friability is also a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 or more), placing them in a rotating plexiglass drum in which they are lifted during replicate revolutions by a radial louver, and then dropped through the diameter of the drum. After replicate revolutions, the tablets are reweighed and the percentage of powder "rubbed off" or

broken pieces is calculated. Friability in the range of about 0% to 3% is considered acceptable for most drug and food tablet contexts. Friability which approaches 0% is particularly preferred.

Tablets of insufficient hardness exhibit capping and/or lamination and can easily break apart or disintegrate under normal handling and packaging conditions. Tablets of insufficient hardness cannot be used for lozenges or mints which are designed to be sucked in the mouth, releasing the active ingredients or flavor over time, and may have an undesirable powdery, grainy or coarse mouthfeel.

Lactitol is not considered to be directly compressible, ie. crystalline lactitol cannot be compressed into tablets of sufficient hardness and low friability. Therefore, in order to utilize lactitol in tablets, a variety of approaches to impart these characteristics have been used, without complete success.

When milled lactitol monohydrate having a mean particle size of about 65 microns was tabletted on a Manesty F3 press utilizing 1 % magnesium stearate as the lubricant, tablets with acceptable hardness and friability were obtained. However, the coefficient of tablet weight variance was excessive (>4%). The high variance was attributed to the poor flow characteristics of the milled lactitol. The addition of up to about 8% talc to the milled lactitol sufficiently improved product flow and reduced tablet weight variance to an acceptable level, at the expense of poor tablet friability (>67%).

When crystalline lactitol monohydrate having a mean particle size of about 500 micron was tabletted on a Manesty F3 press utilizing 1 % magnesium stearate as lubricant, acceptable flow characteristics were observed and uniform tablet weights were obtained. However, tablet hardness was marginal at best and tablet friabilities were excessive.

Attempts to combine milled and crystalline lactitol monohydrate in a 1:1 weight ratio resulted in tablets with marginally acceptable hardness, higher than acceptable friability and less than desired flow characteristics and table weight uniformity.

When crystalline anhydrous lactitol of varying mean particle sizes is tabletted, tablets with initially acceptable hardness and friability may be obtained. However, presumably because of anhydrous lactitol's tendency to absorb atmospheric water and move towards the monohydrate form, the tablets become notably softer upon even mild ambient storage conditions.

The present invention contemplates a directly compressible, non-cariogenic free-flowing lactitol granulate having an average particle size of up to 500 microns. The granulate comprises lactitol and a physiologically acceptable, non-cariogenic binder; acceptable binders include sugar alcohols, polymerized reducing sugars, alkali carboxymethylcellulose, hydrogenated starch hydrolysate, hydroxypropylcellulose, physiologically acceptable cellulose derivatives, PVP, gum arabic and other physiologically acceptable gums. The particularly preferred sugar alcohol binder is lactitol. Particularly preferred polymerized reducing sugar binders are maltodextrin and modified polydextrose, and the particularly preferred alkali carboxymethylcellulose binder is sodium carboxymethylcellulose. The granulate can also include other sweeteners.

A further embodiment of the invention includes a directly compressible, non-cariogenic, free-flowing lactitol granulate, which comprises milled lactitol with a lactitol binder. The binder is present in the granulate at levels of between about 2% to about 30% by weight, with levels of 5% to 15% being preferred, and levels of 10% to about 15% being particularly preferred.

The invention also contemplates a relatively stable, non-cariogenic consumable tablet, formed by direct compression means comprising lactitol, and a physiologically acceptable, non-cariogenic binder. The tablet may also include other excipients, including micro-crystalline cellulose, physiologically acceptable cellulose derivatives, starch, food grade starch derivatives, and non-cariogenic sugar alcohols. The tablet may also include intense sweeteners. Intense sweeteners taken from the group consisting of dipeptide sweeteners, saccharin, acesulfame K, stevioside, cyclamate, sucralose and neohesperidin dihydrochalcone are preferred.

The present invention also contemplates a method for the production of a directly compressible, free-flowing, non-cariogenic lactitol granulate, which consists of granulating milled lactitol with a mean particle size of less than about 300 microns with a physiologically acceptable, non-cariogenic binder. The binders include those mentioned above, with a particularly preferred binder being lactitol. In a preferred embodiment, the lactitol is utilized in an aqueous solution in concentration of between about 30% to about 60% by weight, with concentrations of between about 45% to about 55% being particularly preferred.

The invention is described below in greater detail, partly with reference to the accompanying drawing, wherein

Figure 1 shows the stability of tablets made from a lactitol granulate compared to tablets made from a commercially available tabletting grade mannitol, and

Figure 2 shows the results of compression studies comparing the hardness of tablets made from a lactitol granulate of the present invention, tablets made from a commercially available tabletting grade mannitol, and lactose.

The granulate of the present invention exhibits excellent flowability and compressibility, when used in typical tabletting equipment, such as a Manesty Express 20 rotary tabletting press, or other tabletting presses which are known to one of ordinary skill in the art. The preferred lactitol used to form the granulate is lactitol milled to an average particle size of less than about 300 microns, preferably with a mean size of between about 30 - 200 microns, with a mean size of between about 50 to about 90 microns being particularly preferred. Crystalline lactitol can be milled, ground or otherwise comminuted to reach the preferred particle size. The crystalline lactitol may be provided in the form of anhydrous lactitol, as lactitol mono, di or tri hydrate in pure crystalline form or as solid mixtures of said hydrated and/or anhydrous species. The preferred crystalline lactitol is lactitol monohydrate.

The lactitol may also be combined for granulation with other non-cariogenic polyols, such as xylitol.

The binder contemplated by the present invention is a physiologically acceptable, non-cariogenic binder. Surprisingly and unexpectedly, an aqueous lactitol solution functions as an excellent binder in this context. Lactitol is not generally known as a binder. However, an aqueous lactitol solution of between about 30% - 60% (by weight) has been found to work extremely well as a binder in the present invention. An aqueous solution of lactitol of between about 45% - 55% (by weight) is preferred, with a solution of between about 49% - 51 % (by weight) being particularly preferred. The resulting granulate is thus comprised solely of lactitol, thereby allowing full expression of all of its taste and technological benefits. The crystalline form of the lactitol binder is not critical.

Another binder is an alkali carboxymethylcellulose such as sodium carboxymethylcellulose. Sodium carboxymethylcellulose can be utilized in a wide range of cosmetic, food, pharmaceutical and industrial applications, but has heretofore not been utilized as a binder with lactitol in tabletting contexts. Sodium carboxymethylcellulose is available from Aqualon Company, Wilmington, Delaware. Sodium carboxymethylcellulose is a cellulose ether produced by

reacting alkali cellulose with sodium monochloroacetate under controlled conditions. Sodium carboxymethylcellulose is available in food, pharmaceutical and standard grades with varying degrees of substitution (from 0.38 to 1.4) and viscosity characteristics in solution with water.

Other acceptable binders include reducing sugar polymers such as maltodextrin and the modified polydextrose described, for instance in EP Patent Application 90300577.5. A further binder is hydrogenated starch hydrolysate. Hydrogenated starch hydrolysate is the catalytically hydrogenated product of high maltose syrup and is commercially available from a wide variety of sources. Other functional binders can include hydroxypropylcellulose, other physiologically acceptable cellulose derivatives, polyvinylpyrrolidone (PVP), gum arabic and other physiologically acceptable gums.

The level of lactitol binder in the final dried product (as a percentage of dry weight) will be between about 2% to about 30%, with a preferred percentage of between about 5% to about 15%, with a percentage of about 10% to about 15% being particularly preferred.

Granulation of the lactitol and binder can be achieved with any of the standard means of granulation available. Suitable commercial granulators or granulating systems include the Lodige horizontal blender (Gebruder Lodige GmbH) in combination with a fluidized bed dryer, the Glatt vertical fluidized bed granulator (Glatt GmbH, Binzen, West Germany), the Aeromatic vertical fluidized bed granulator (Aeromatic AG, Bubendorf, Switzerland) and the Schugi granulator (Schugi, BV, Lelystad, Holland). Other granulation devises commonly known to those skilled in the art can be utilized in the practice of our invention.

The produced and dried granulate is usually screened following the granulation step to remove coarse particles. A suitable sieve size for this purpose is a 16 mesh (1.2 mm) screen. The coarse particles can either be reworked, milled or dissolved for further use.

The granulate can be utilized as a sweetening, flavor or bulking agent and/or as a diluent in food and pharmaceutical contexts alone, or in combination with other sweeteners (such as intense sweeteners), other polyols and/or other binding agents.

The granulate of the present invention can be used as an excipient in a tablet, alone or in combination with other excipients, lubricant(s), flavoring agents, and/or diluents. The concentration range of the granulate can be from about 5% to about 99.5% by dry weight; other excipients include microcrystalline cellulose, various cellulose derivatives, starch, various starch derivatives, and non-cariogenic sugar alcohols.

Example 1

Utilizing a SWG 15 Glatt Fluid Bed Granulator equipped with a screen at the bottom of the bowl and an exiting granulation comil (Quadro Comil, Model 197-1-064 with a size 2A-.04R031/37 screen, approximately 65 micron milled lactitol monohydrate was granulated with the aid of a 50% (w/w) aqueous lactitol binder which was prepared and maintained under ambient conditions. Three granulated lactitol products were prepared: A) 6% binder (dry weight basis, dwb); B) 12% binder (dwb); and C) 18% binder (dwb). The conditions of manufacture were as follows: inlet temperature (about 80 °C); atomizing air pressure (about 5 bar); binder spray rate (about 110 ml/min); and outlet air temperature (about 34 °C during the processing cycle and about 44 °C at the end of drying cycle). Products B and C were produced with an air flow of about 5.6 m^3/min (200 cfm), while product A was produced with an air flow of about 7.0 m^3/min (250 cfm). Each product exhibited satisfactory flow properties; moisture levels of about 4.6%, loose bulk densities of about 0.58 g/ml, and tapped densities of about 0.68 g/ml. Approximately 550 mg, 11 mm (7/16 in) flat faced beveled edge tablets were prepared utilizing each granulated product at 2.0 tons compression force at a rate of 1000 tablets/minute utilizing a Manesty Express 20 rotary tabletting press. Each product yielded pleasant tasting tablets which exhibited excellent hardness and acceptable friability. The hardness of tablets from the respective products were as follows: A about 231 N (33 Strong Cobb Units, S.C.U.); B about 238 N (34 S.C.U.); and C about 154 N (22 S.C.U.).

Example 2

Lactitol granulate from Example 1B and a commercial granular mannitol were compressed into 15mm flat faced beveled edge tablets of similar hardness (about 20 scu) using 1 % magnesium stearate as the lubricant. The tablets were stored over a 23 day period at about 20 °C and about 75 % relative humidity. Moisture increase was monitored. As illustrated by Figure 1, the lactitol tablets exhibited a moisture increase of only about 0.1 % while the commercial mannitol product exhibited a moisture increase of about 1.0%.

Example 3

The lactitol granulates from Examples 1A-C exhibited mean particle sizes which were below about 200 microns. In an effort to increase the mean particle size of the lactitol granulate, milled lactitol monohydrate was granulated with a 50% (w/w) ambient lactitol solution using the equipment of Example 1 under the following conditions: air flow 7 m^3/min (250 cfm); inlet temperature (about 85 °C); atomizing air pressure (about 2.5 bar); spray rate (about 250 ml/min); spray time (about 11 minutes); and outlet temperature (about 38 °C during the

processing cycle and about 45 °C during the drying cycle). The binder level of the final granulate was about 12% on a dry weight basis. The resulting granulate exhibited excellent flow properties and was essentially dust free. The mean particle size was about 390 micron. Other granulate attributes were as follows: moisture (about 4%); loose bulk density (about 0.45 g/ml); tapped bulk density (about 0.54 g/ml).

Example 4

A further granulate was prepared as in Example 3. The resulting granulate had a mean particle size of about 300 micron. The granulate exhibited excellent flow properties, a moisture level of about 5%, a loose bulk density of about 0.55 g/ml and a tapped density of about 0.64 g/ml. The granulate was subjected to various comparative evaluations versus both a commercial directly compressible mannitol and a commercial directly compressible lactose. The comparative evaluations included 1) compression profiles; 2) preparation of ascorbic acid (vitamin C) tablets; and 3) assessment of excipient dilution potential utilizing non-granular acetaminophen (APAP) powder as the diluent.

The compression profiles were conducted on 11 mm (7/16 in) flat faced beveled edge tablets having a mean weight of about 600 mg. Magnesium stearate was utilized at a 0.5% level as the tabletting lubricant. Tablets were prepared on a Manesty Express 20 rotary press. The results of the compression studies, which are illustrated in Figure 2, suggest that the lactitol granulate performs in a manner which is superior or similar to the two comparative commercial excipients.

The approximate 600 mg tablets containing ascorbic acid were prepared as above utilizing 10% (w/w) ascorbic acid, 87.5% excipient, 2.0% Ac-di-sol and 0.5% magnesium stearate. A compression force of 1.3 tons was utilized. Each excipient produced acceptable tablets as illustrated in Table 1.

Table 1

Ascorbic Acid Tablet Characteristics

Property	Lactitol	Mannitol	Lactose
Hardness, Kp	8.4-16.8	5.7-11.5	9.4-16.0
Thickness, mm	4.65-4.72	4.82-4.90	4.87-4.92
Weight Variance, n = 10			
Mean. mg	605	605	605
Std. Dev.	4.09	3.94	3.05
RSD, %	0.74	0.65	0.51
Friability, %	0.82	0.74	0.24

Each excipient was evaluated for dilution potential in conjunction with either 10% or 30% APAP as diluent. Magnesium stearate was utilized as lubricant at the 0.5% level. Tablets were prepared as above utilizing compression forces in the range of 1.3-2.0 tons. Each excipient exhibited similar dilution potentials as illustrated in Table II.

Table II

Dilution Potential Characteristics

Property	Lactitol		Mannitol		Lactose	
	10%APAP	30%APAP	10%APAP	30%APAP	10%APAP	30%APAP
Hardness, Kp	6.5-11.7	2.9-4.2	6.6-12.5	3.6-5.4	6.4-15.4	4.4-9.9
Thickness, mm	4.78-4.90	4.74-4.89	4.95-5.02	5.12-5.19	4.59-4.65	4.98-5.11
Weight Variance, n= 10						
Mean, mg	597	591	606	601	604	596
Std. Dev.	6.6	11.0	6.4	5.9	6.5	14.0
RSD, %	1.1	1.9	0.8	1.0	1.5	2.9
Friability, %	3.4	11.0	3.1	12.7	1.1	7.1

Example 5

The lactitol granulate was produced on a plant scale utilizing a WSG500 Glatt Fluid Bed Granulator equipped with a 16 micron wire mesh at the bottom of the bowl. The granulate was milled through a Quadro Comil installed on the granulator with a 0.075H37/60 screen size. Milled lactitol monohydrate (with an average particle size of about 65 micron) was bound with 12% dry weight basis ambient lactitol solution (50% w/w). General granulation conditions were as follows: air flow [initial about 73 m^3/min (2600 cfm), final about 78 m^3/min (2800 cfm); inlet air temperature (about 85-90 °C) outlet air temperature (about 30-33 °C); spray rate (about 3 liters/min); and final cooling temperature (about 29 °C). The granulate had a mean particle size of about 280 microns and exhibited excellent blow properties while being essentially dust free. The moisture level of the granulate was about 5%. The loose and tapped bulk densities were about 0.57 g/ml and 0/65 g/ml respectively. When compressed on a Manesty Express 20 rotary press to form 600 mg flat faced beveled edge tablets 11 mm (7/16 in) in diameter at about 1.5 tons compression force using 0.5% magnesium stearate as lubricant, the resulting tablets exhibited a pleasing taste and mouthfeel with no aftertaste. Tablet hardness was about 25 kilopounds (Kp), tablet weight variation was about 1 % RSD (relative standard deviation) and tablet friability was less than 1 %.

Example 6

A simple kitchen multiple functions mixer (Moulinex) was used to prepare lactitol granulates on a small scale (200 g batches) using different binders. The process is comparable to granulation using commercial high speed mixers/granulators.

Aqueous solutions of various binders were prepared in advance as follows:
- lactitol 60% w/w
- gelatine 10% w/w
- hydroxypropylcellulose 5% w/w
- PVP 3% w/w

The combinations tested are presented in Table III below.

TABLE III

Lactitol, g	Binder Type	g	%*	Water added, g
200	lactitol	17.4	8.00	11.6
150	gelatine	0.8	0.53	7.2
150	HPC	0.35	0.23	6.65
200	PVP	0.3	0.15	9.7

* % is counted as % of total solids, water not taken into account

The various binder solutions were slowly added to the until granules were formed. The granulates were dried in the oven at 60 °C.

The dispersibility of the granulates was assessed visually by dispersing a teaspoon of the granulates into 100 ml of tap water.

The granules formed using the lactitol solution as a binder were the best for the dispersion and also the taste was the best when they were tested. For the batches with binders of low water solubility granules (e.g. gelatine) the dispersion was worse than for lactitol bound granules.

For tabletting the granulates were mixed with 1 % of magnesium stearate for 2 minutes in a Turbula mixer. The lubricated granulates were tabletted on single punch machine (Manestry) using a 12.7 mm (0.5 in) diameter punch. The strong lactitol granules tabletted very well with the PVP tablet being the strongest.

Example 7

Crystalline lactitol milled to an average particle size of 50 μm (Lactitol CM50, Xyrofin Oy Kotka, Finland) was placed in the mixing bowl of a Moulinex multi purpose mixer.

Binder solutions were made as follows:

A 10% solution of maltodextrin was produced by dissolving 20 g of Maltodextrin C*Pur01915 (produced by Cerestar) in 180 g water. 8.2 g of this solution was used for 150 g of milled lactitol. A 3% solution of PVP was produced by dissolving 6 g of PVP K30 (produced by ISP) in 194 g water. 10.0 g of this solution was used for 200 g of milled lactitol. A 60% solution of lactitol was produced by dissolving 120 g of Lactitol MC (produced by Xyrofin Oy) in 80 g water. 30.0 g of this solution was used for 200 g of milled lactitol.

Binder solution was added to the lactitol via a syringe, whilst the lactitol was being mixed. Thereafter the mix was sieved through a domestic sieve (Approx 1 mm aperture) onto a foil lined baking tray. The mix was then placed in an oven set to 40 °C overnight to dry. The dried granulate was sieved through a domestic sieve prior to tabletting.

1% magnesium stearate was used for lubrication. The granulate was then tabletted on a Manesty 2C single punch press using a 15 mm diameter flat-faced bevelled edge punch.

The compression force was adjusted by altering the drop of the top punch. Tablet hardness was measured using a Key Instruments tablet hardness tester which measures the force required to break the tablet across its diameter. Ten tablets were tested and an average reading recorded.

The thickness of ten tablets was measured using a micrometer gauge. The average of ten tablets is recorded. Ten tablets were weighed individually and an average recorded.

Tablet friability was measured using a Key Instruments friability tester. Ten tablets were dropped 100 times and the percentage weight loss recorded. Any tablets that are badly chipped are removed prior to weighing.

Results

All of the above granulates produced acceptable tablets with maximum hardness values greater than 350N. All of the tablets produced had acceptable friability results.

Table V summarizes the tabletting results.

TABLE V

Compression*	40	40.5	39.5	40	40.5	39.5	40	40.5
Binder	Malto-dextrin	Malto-dextrin	PVP	PVP	PVP	Lactitol	Lactitol	Lactitol
Weight (g)	1.109	1.068	1.156	1.194	1.209	1.215	1.237	1.235
SD	0.017	0.01	0.009	0.005	0.015	0.014	0.008	0.009
Rel SD(%)	1.556	0.932	0.787	0.429	1.212	1.156	0.638	0.767
Thickness (mm)	4.386	4,209	4.612	4.671	4.717	4.778	4.839	4.816
SD	0.044	0.032	0.023	0.02	0.054	0.044	0.028	0.038
Rel SD(%)	1.014	0.762	0.491	0.431	1.149	0.926	0.571	0.784
Hardness (N)	343(394)	335(395)	302(357)	383(390)	364(399)	357(373)	359(387)	384(381)
SD	62(19)	51(10)	49(13)	19(23)	48(25)	34(8)	55(9)	20(10)
Rel SD(%)	18.2(4.8)	15.2(2.4)	16.2(3.8)	4.9(5.9)	13.2(6.3)	9.5(2.1)	15.2(2.3)	5.2(2.5)
Friability (10 tabs)	0.24	0.42	0.3	0.44	0.37	0.4	0.27	0.47

The figures shown in brackets are those taken from analysis performed during production.
All other results are from analysis performed ~24 hours after production.

* Compression forces cannot be compared between mixes.

Example 8

A 50/50 mixture of lactitol and xylitol was granulated by mixing 6 kg of each polyol in a bowl. The granulation was made in a WSG 15 Glatt granulator using sodium carboxymethylcellulose as a binder at 60 °C. The concentration of the NaCMC was 1.5 %.

The compressibility properties of the granulation was determined using a Manesty Express 20 rotary press. Two kilograms of the granulated product were screened through # 20 mesh screen and blended with 10 grams of magnesium stearate for 5 minutes in a Hobart blender.

Compression was done under the following conditions:

Machine:	Manesty Express 20
Tooling:	11 mm (7/16") flat face beveled edge round tablet punches and dies
Tablet weight:	550 mg
Compression Force:	1.0-3.0 Tons

The compression hardness of the tablets was about 237 N (33.9 S.C.U.).

The foregoing general discussion and experimental examples are intended to be illustrative of the present invention, and are not to be considered limiting. Other variations within the spirit and scope of this invention are possible, and will present themselves to those skilled in the art.

Claims

1. A directly compressible, non-cariogenic free-flowing lactitol granulate having an average particle size of up to 500 microns, which comprises lactitol and a physiologically acceptable, non-cariogenic binder in the range of about 2% to about 30% by dry weight taken from the group consisting of sugar alcohols, polymerized reducing sugars, alkali carboxymethylcellulose, hydrogenated starch hydrolysate, hydroxypropylcellulose, physiologically acceptable cellulose derivatives, PVP, gum arabic and other physiologically acceptable gums.

2. The directly compressible granulate of claim 1 wherein said lactitol comprises milled crystalline lactitol monohydrate, dihydrate, trihydrate, anhydride and/or crystalline or precipitated mixtures thereof.

3. The directly compressible granulate of claim 2, wherein said milled lactitol is lactitol monohydrate.

4. The directly compressible granulate of claim 1 wherein said sugar alcohol binder is lactitol.

5. The directly compressible granulate of claim 1 wherein said alkali carboxymethylcellulose binder is sodium carboxymethylcellulose.

6. The directly compressible granulate of claim 1 which additionally includes an intense sweetener, such as dipeptide sweeteners, saccharin, acesulfame K, stevioside, cyclamate, sucralose and/or neohesperidin dihydrochalcone.

7. The directly compressible granulate of claim 1 which additionally includes another sugar alcohol, such as xylitol.

8. The directly compressible, non-cariogenic, free-flowing lactitol granulate of claim 1, wherein said binder is present in the granulate at levels of 10% to about 15% by dry weight.

9. A directly compressible, non-cariogenic, free-flowing lactitol granulate, which comprises milled lactitol with a lactitol binder, wherein said binder is present in the granulate at levels of between about 2 % to about 30 % by dry weight.

10. The directly compressible granulate non-cariogenic, free-flowing lactitol granulate of

claim 9, wherein said milled lactitol comprises lactitol monohydrate, lactitol dihydrate, lactitol trihydrate, anhydrous lactitol or a mixture thereof.

11. The directly compressible non-cariogenic, free-flowing llctitol granulate of claim 10, wherein said milled lactitol is lactitol monohydrate.

12. The directly compressible, non-cariogenic, free-flowing lactitol granulate of any one of claims 9 to 11, wherein said binder is present in the granulate at levels of between about 5% to about 15 % by dry weight.

13. A relatively stable, non-cariogenic consumable tablet formed by direct compression means comprising lactitol and a physiologically acceptable non-cariogenic binder taken from the group consisting of sugar alcohols, polymerized reducing sugars, alkali carboxymethylcellulose, hydrogenated starch hydrolysate, hydroxypropylcellulose, physiologically acceptable cellulose derivatives, PVP, gum arabic and other physiologically acceptable gums.

14. The consumable tablet of claim 13 wherein said sugar alcohol binder is lactitol.

15. The consumable tablet of claim 13 which additionally includes one or more other excipients.

16. The consumable tablet of claim 15, wherein said excipients are taken from the group consisting of microcrystalline cellulose, physiologically acceptable cellulose derivatives, starch, food grade starch derivatives, and non-cariogenic sugar alcohols.

17. The consumable tablet of claim 16, wherein said non-cariogenic sugar alcohol is xylitol.

18. The consumable tablet of claim 13 which additional includes an intense sweetener taken from the group consisting of dipeptide sweeteners, saccharin, acesulfame K, stevioside, cyclamate, sucralose and neohesperidin dihydrochalcone.

19. A method for the production of a directly compressible, free-flowing non-cariogenic lactitol granulate which consists of granulating milled lactitol with a mean particle size of less than about 300 microns with a physiologically acceptable, non-cariogenic binder taken from the group consisting of sugar alcohols, polymerized reducing sugars, alkali carboxymethylcellulose, hydrogenated starch hydrolysate, hydroxypropyl- cellulose, physiologically

acceptable cellulose derivatives, PVP, gum arabic and other physiologically acceptable gums and screening the resulting granulate.

20. The method of claim 19 wherein said sugar alcohol binder is lactitol.

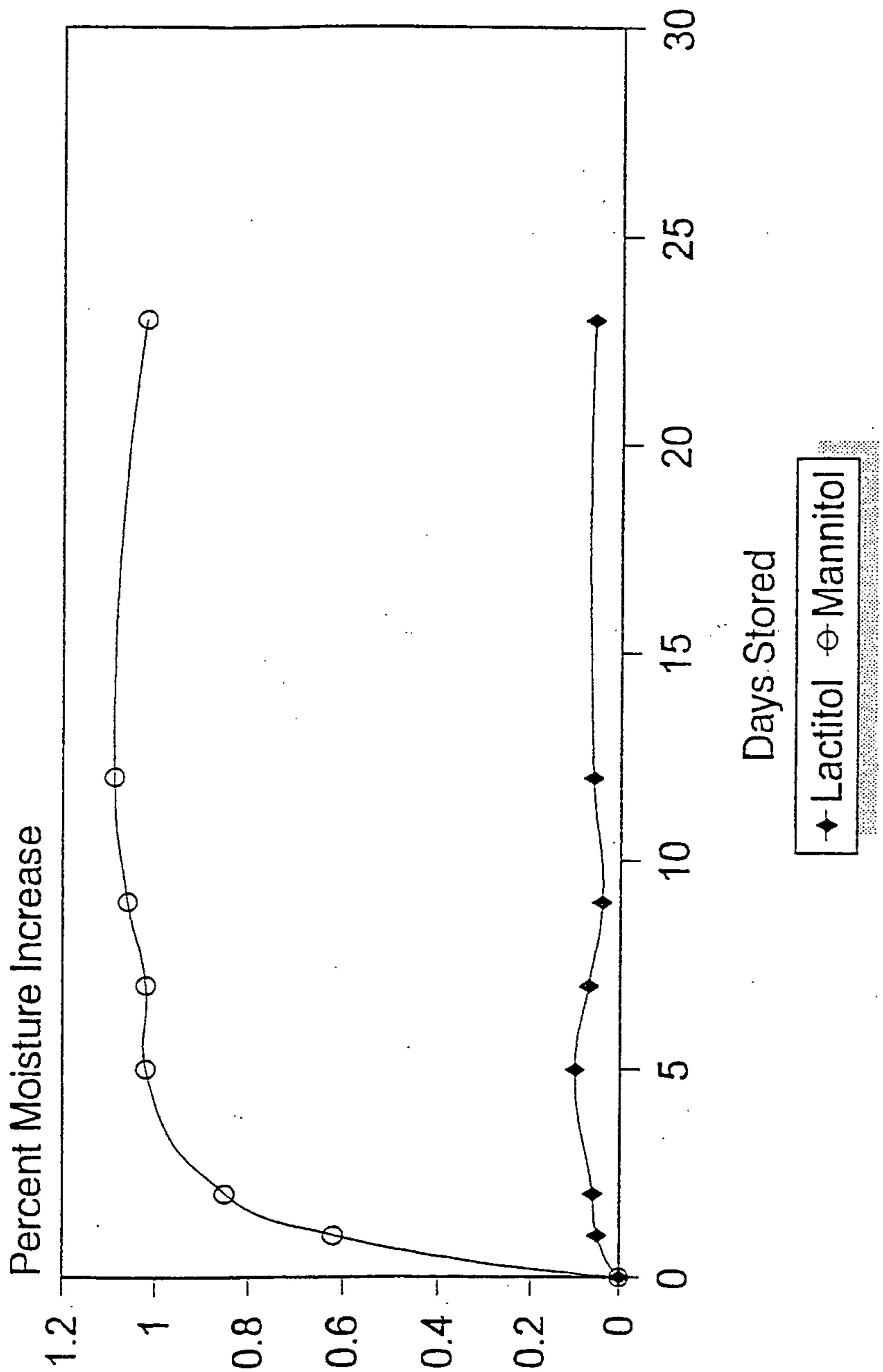
21. The method of claim 20 wherein said lactitol binder is utilized in an aqueous solution with lactitol in a concentration of between about 30% to about 60% by weight.

22. The method of claim 20 wherein said lactitol binder is utilized in an aqueous solution with a lactitol concentration of between about 45% to about 55% by weight.

23. The method of claim 20 wherein said lactitol binder is utilized in an aqueous solution with a lactitol concentration of between about 49 % to about 5 1 % by weight.

24. The method of claim 19 wherein said granulate has a mean particle size of less than about 500 microns.

25. The method of claim 19 wherein said granulate has a moisture content of less than about 7% by weight.



20 C, 75% Relative Humidity

FIG 1

2/2

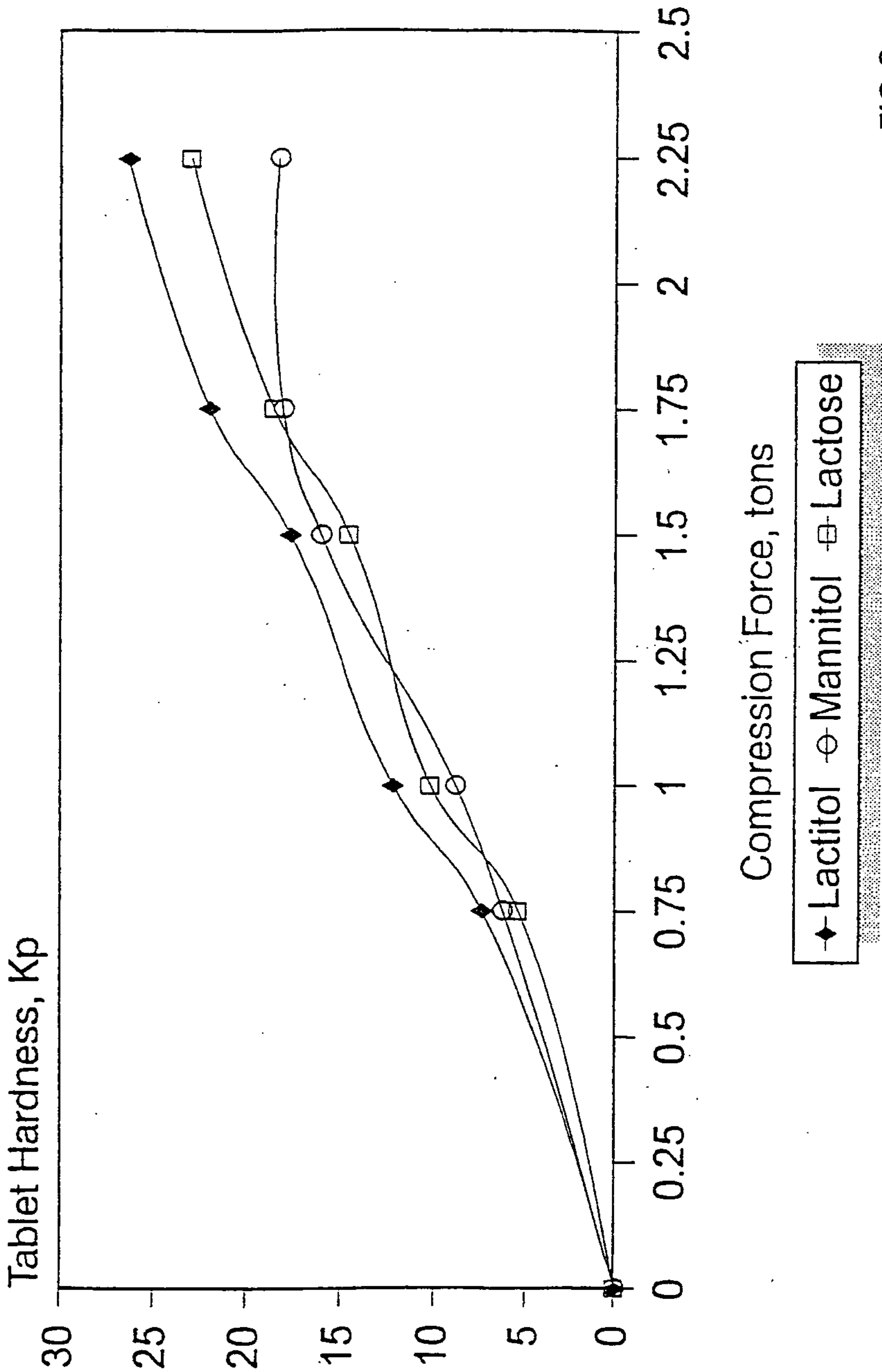

Tablet Hardness, Kp
30
25
20
15
10
5
0
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2
2.25
2.5
Compression Force, tons
Lactitol
Mannitol
Lactose

FIG 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 97/00548

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/20, A61K 47/26, A61K 9/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, USPATFULL, EMBASE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5204115 A (PHILIP M. OLINGER ET AL), 20 April 1993 (20.04.93), column 7, line 16 - line 28; column 7, line 42 - column 8, line 40, claim 37 --	1-25
A	US 5536526 A (JOUKO VIRTANEN ET AL), 16 July 1996 (16.07.96) --	1-25
P,X	Dialog Information Services, File 351, Dialog accession no. 011488285, Nippon Shinyaku Co Ltd: "Highly water-soluble solid medical fast-dissolving tablet - produced by kneading lactitol with water and compressing"; & JP,A,9216816, 19970819 (Basic) --	1-25

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1997	02 -01- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/97

International application No.
PCT/FI 97/00548

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		WO 9210168 A	25/06/92
US 5536526 A	16/07/96	US 5616361 A	01/04/97